Remarks

Remarks are arranged in numerical or subject headings as set forth in the non-final office action mailed on January 5, 2009.

Status of the Application

Claims 1-4 and 7-11 are pending and rejected in current non-final office action. Claims 5-6 are withdrawn from consideration.

Claim Rejections – 35 USC §102 and 103

The rejection of claims 1-3, 7, and 9-10 under 35 USC 102(b) as being anticipated by Paterniti et al (WO 9805331) is maintained. The rejection of claim 4 under 35 USC 103(a) as being unpatentable over Paterniti et al (WO 9805331) is maintained. The rejection of claim 8 under 35 USC 103(a) as being unpatentable over Barelli et al (US 5922796) in view of Ko et al is maintained.

In response to current office action, claim 1 is amended to specifically point out the invention that excludes any active ingredients other than the two recited in the claim.

As stated on page 5, second paragraph, "current invention involves a pharmaceutical composition containing a combination of a biguanide, preferably metformin and non-glucose-lowering fibrates, preferably gemfibrozil or ciprofibrate, as **active agents**". It is well known common knowledge that, in a pharmaceutical composition, any component other than the active agent is regarded as an inactive ingredient. See definitions provided by US Food and

Drug Administration (FDA): "[a]ccording to 21 CFR 210.3(b)(8), an **inactive ingredient** is any component of a drug product **other than the active ingredient**" (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm). Since instant application specifically points out that only the cited agents are used as "**active agents**", ingredients used in instant invention other than the active agents are regarded as "**inactive ingredients**" by aforementioned common knowledge.

Further, it is stated in specification that "the invention involves a pharmaceutical composition comprising, as active agents, (1) metformin in one of its pharmaceutically acceptable form, and (2) a lipid-improving agent selected from gemfibrozil and ciprofibrate in one of their pharmaceutically acceptable form, in combination with one or more pharmaceutically acceptable excipients" (Page 6, 2nd paragraph). It is commonly known that "[p]harmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form" (International Pharmaceutical Excipients Council (IPEC), available at following URL: http://www.ipecamericas.org/public/faqs.html#question1). This clearly supports that the amended claim 1 consists of the claimed active agents and one or more inactive ingredients.

Based on the aforementioned facts, current amendment to claim 1 does not introduce any new matter and is supported by the specification as originally filed and by well known common knowledge.

The currently amended claim 1 requires two active agents, namely (1) a glucose-lowering agent metformin in one of its pharmaceutically acceptable forms, and (2) a lipid-improving agent selected from non-glucose-lowering fibrates, and one or more pharmaceutically acceptable **inactive** ingredients. Currently amended claim 1 excludes any active ingredients other than the (1) and (2) recited in the claim.

As stated in current Office Action, the Examiner agrees that instant claim 1 now recites "consisting of" which excludes the presence of any non-recited elements (Page 2, last paragraph, current Office Action). PPARgamma agonist is a well known active ingredient as evidenced by over 1000 publications in PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez). Currently amended claim 1 excludes such active ingredients and therefore is distinctive from what disclosed in the cited references.

Applicants respectfully submit that current amendment to claim 1 overcomes rejections maintained in current office action. Allowance of amended claim 1 is respectfully requested.

Claims 2, 3, 7 and 9-10 are dependent from claim 1. Limitations of claim 1 are read into these claims. Since any additional active ingredients are excluded, these claims are equally distinctive from the cited references. Applicants respectfully request allowance of these claims.

Claim 8 is canceled.

New Ground of rejection

Claim Rejections – 35 USC § 112

Claims 9 and 10 are rejected under 35 USC § 112, first paragraph.

Claim 9 is amended to use the wording "treating". Applicants respectfully submit that the amendment overcomes the rejection of the claims.

With the aforementioned amendment, applicant respectfully request that the rejections on claims 9 and 10 be withdrawn.

Claim Rejections – 35 USC §103

Claims 1-4, 7-11 are rejected under 35 USC 103(a) as being unpatentable over Weintraub et al.

Weintraub et al specifically teach that **gemfibrozil** [Applicant's *Note: Weintraub et al seemed using "gemfibrizil" and "gemfibrozil" interchangeably*] is used for **patients with type IV HLP**, while **metformin** is used for patients with **non-diabetic subject who were glucose intolerant** (Weintraub, et al, page S72, last two lines in left column to first line in right column, and Table 1 and Table 2). The two drugs are used for two very different types of patients. While Weintraub et al teach that **gemfibrozil** effectively reduced PPLp in **patients with type IV HLP**, Weintraub et al fail to teach the effect of metformin on PPLp in **patients with type IV HLP**. The Examiner's statement "Weintraub et al discloses that gemfibrozil and metformin are shown to be beneficial for the clearance of PPLp in hypertriglyceridemic patients (see abstract; Discussion)" (1/5/2009 Office Action, page 8 paragraph 2) is incorrect. The original texts read as "In conclusion gemfibrozil, benzafibrate and metformin were shown to be beneficial in the

clearance of PPLp in hypertriglyceridemic patients, subject with isolated low HDL-C levels and nondiabetic glucose intolerant subjects, respectively" (Abstract) and " .... patients, and the effect of gemfibrozil, benafibrate and metformin, respectively, on PPLp levels" (page S72, left column, middle of 3rd paragraph). The texts clearly show the meaning of "gemfibrozil in hypertriglyceridemic or type IV HLP patients", "benzafibrate in subject with isolated low HDL-C levels" and "metformin in nondiabetic glucose intolerant subjects or insulin resistance patients". There is no teaching in Weintraub et al on the effect of metformin on the clearance of PPLp in hypertriglyceridemic patients. Furthermore, Weintraub et al teach that gemfibrizil (1200 mg/day) shows effect in **6 weeks** while metformin shows effect in **3 months** with 850 g [seems to be 850 mg, Applicants' note] twice a day dosage (page S72, right column, second paragraph).

Weintraub et al teach that the two drugs take effect in different time frame with metformin requiring longer time, such as **3 months (about 12 weeks**, twice as long as that for gemfibrozil) to show medical effects. Based on teaching from Weintraub et al, the two drugs will take different time to show medical effect therefore teaching away from combining the two drugs into one pharmaceutical composition.

In fact, there is no teaching in Weintraub et al on what would be the medical effect at **6 week time** point if metformin were added to gemfibrizil for type IV HLP patients. Conversely, there is no teaching in Weintraub et al on what would be the medical effect at **3 month time point** if gemfibrizil were added to metformin for the non-diabetic glucose intolerant patients. Further, there is no

teaching in Weintraub et al on what would be the medical effect if **both** metformin and gemfibrizil were administered to the type IV HLP patients. Conversely, there is no teaching in Weintraub et al on what would be the medical effect if **both** metformin and gemfibrizil were administered to the non-diabetic glucose intolerant patients. Even further, there is no teaching in Weintraub et al on what would be the medical effect if **both** metformin and gemfibrizil were administered to a diabetic patient. In each of the aforementioned aspects, medical effect is uncertain. There is no clear indication on what would be the medical effect for each of the situations described above.

With the lack of teaching in those aforementioned aspects and the lack of predictability, there is no teaching, suggestion or motivation for one of ordinary skill in the art to combine the two drugs at the time the invention was made.

As a further support of non-obviousness, Weintraub et al did not combine both drugs in any single patient or group of patients even with the possession of both gemfibrozil and metformin. Instead, Weintraub et al teach the use of one drug to treat one specific disorder. Such fact provides a secondary support that it would not have been obvious to one of ordinary skill in the art to combine the two drugs at the time the invention was made. In fact, Weintraub et al should have been considered experts having advanced skill more than one of ordinary skill in the art.

Even further, Applicants unexpectedly discovered that the combination of the two claimed active agents exhibits unexpected synergetic glucose lowering

effect (Examples 1 and 2). There is no teaching in Weintraub et al on the synergetic effect.

In conclusion, Weintraub et al fail to provide teaching, suggestion or motivation to one of ordinary skill in the art to combine the two drugs and to use on diabetic patients. It would have not been obvious to one of ordinary skill in the art to combine the two drugs at the time the invention was made. Further, instant invention has unexpected effect.

Regarding claim 11, Paterniti clearly disclosed a composition comprising (1) a pharmaceutically effective amount of a **PPARgamma agonist AND** a **PPARalpha agonist**; and (2) a pharmaceutically acceptable carrier. In a preferred embodiment, the composition can **also** include metformin (Page 13, lines 19-29, WO9805331). That means the composition always comprises **PPARgamma agonist AND PPARalpha agonist**. As mentioned before, currently amended claim 1 excludes **PPARgamma agonist**. Based on reasons previously presented and agreed by the Examiner, instant invention excludes the presence of non-recited elements, such as **PPARgamma agonist** and is distinctive over Paterniti et al.

With aforementioned reasoning, Applicants respectfully request the rejections to the claims be withdrawn and claims 1-4 and 7-11 be allowed.

Conclusion

In view of the foregoing, allowance of the pending claims is respectfully requested.

Respectfully submitted,

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